

# BioMarin Provides 1.5 years of Clinical Data for Valoctocogene Roxaparvovec Gene Therapy for Severe Hemophilia A at 59th American Society of Hematology (ASH) Annual Meeting Concurrent with NEJM Publication

**Valoctocogene Roxaparvovec Demonstrated Sustained Normal or Near Normal Factor VIII Levels in Severe Hemophilia A for Most Patients at Both Doses in Phase 1/2 Study  
NEJM Publishes One-Year Data for 6e13 vg/kg Dose from Ongoing Phase 1/2 Study  
Global GENER8-1 (Phase 3) Study to Begin Before Year End, and Global GENER8-2 (Phase 3) Study to Begin at the Start of 2018**

SAN RAFAEL, Calif., Dec. 9, 2017 /PRNewswire/ -- BioMarin Pharmaceutical Inc. (NASDAQ: BMRN) announced today an update to its previously reported results of an open-label Phase 1/2 study of valoctocogene roxaparvovec (formerly BMN 270), an investigational gene therapy treatment for severe hemophilia A. The updated results will be presented during an oral presentation at the 59th American Society of Hematology (ASH) Annual Meeting and Exposition by John Pasi, M.B., Ch.B., Ph.D., from Barts and the London School of Medicine and Dentistry and primary investigator for this Phase 1/2 study. On Monday, Dec. 11, 2017, Professor Pasi will present the data, which will include sustained normal or near-normal Factor VIII levels in severe hemophilia A for most patients with a maximum follow up of 19 months. Previously, the company provided updated data on the 4e13 vg/kg dose on Oct. 18, 2017 and on the 6e13 vg/kg dose on July 11, 2017 at a medical meeting.

The data presented at ASH is the most current data (Nov. 16, 2017 cut off) and includes 78 weeks of data for the 6e13 vg/kg dose and 48 weeks of data for the 4e13 vg/kg dose.



"With 1.5 years of data on valoctocogene roxaparvovec, our understanding of this novel gene therapy is considerable, and we are looking forward to drawing on that knowledge in the Phase 3 GENER8 studies, which we expect will begin enrolling patients this month," said Hank Fuchs, M.D., President, Worldwide Research and Development at BioMarin. "We're pleased that this work is being presented in one of the most highly regarded peer reviewed publications and at a pace that is faster than other in vitro gene therapies. This most current data presented at ASH combined with the one-year data published in NEJM will contribute to an increase in understanding within the scientific community about gene therapy in general and specifically about the exciting new developments in a potential one-time treatment for severe hemophilia A."

## Efficacy Data of 4e13 vg/kg Dose as Presented at ASH

As of Nov. 16, 2017, a total of six patients with severe hemophilia A, who had all been treated with prophylactic Factor VIII pre-study, received a single dose of valoctocogene roxaparvovec at 4e13 vg/kg. Since the last data update provided on Oct. 18, 2017, the three patients with the longest follow-up (at week 48) have Factor VIII activity levels that are in or near to the normal range with both median and mean values of 49%. Median annualized bleed and factor VIII use rates for the 4e13 vg/kg cohort were zero after Week 4 when their Factor VIII activity rose above 5%. According to the World Federation of Hemophilia rankings of severity of hemophilia A, the mild hemophilia A range of Factor VIII activity levels is between 5% and 40%, and the normal range of Factor VIII activity levels for people without disease is between 50% and 150%, in each case expressed as a percentage of normal factor activity in blood.

## Factor VIII Levels (%) of 4e13 vg/kg Dose Patients\* by Visit (N=6) at Nov. 16, 2017 data cut

Week**	4	8	12	16	20	24	28	32	36	40	44	48
4e13 vg/kg Dose												
n	6	6	6	6	6	6	6	6	6	3	3	3
Median Factor VIII Level*** (%)	4	15	21	29	34	28	34	42	38	48	56	49

Mean Factor VIII Level*** (%)	<b>5</b>	<b>13</b>	<b>19</b>	<b>26</b>	<b>31</b>	<b>29</b>	<b>31</b>	<b>37</b>	<b>35</b>	<b>50</b>	<b>61</b>	<b>49</b>
Range (low, high)	(2,10)	(3,21)	(6,32)	(5,38)	(7,45)	(7,43)	(4,44)	(4,54)	(4,55)	(37,64)	(45,83)	(38,60)

\*All patients had severe hemophilia A at baseline, defined as less than or equal to 1% of Factor VIII activity levels, expressed as a percentage of normal factor activity in blood.

\*\*Weeks were windowed by +/- 2 weeks

\*\*\* Bolded numbers are in the mild to normal range of Factor VIII activity as defined by the World Federation of Hemophilia, <http://www.wfh.org/en/page.aspx?pid=643> (link current as of Dec. 6, 2017). Factor VIII levels are determined by one-stage assay.

#### Valoctocogene Roxaparvovec Reduces Bleeds and Factor VIII Use: Summary of Annualized Bleeding Rate (ABR) and FVIII Use Rate of 4e13 vg/kg Dose for Patients Previously on Prophylaxis (N=6) at Nov. 16, 2017 data cut

	Before valoctocogene roxaparvovec Infusion	After valoctocogene roxaparvovec Infusion
	Median (mean, SD)	Median (mean, SD)
<b>Annualized Bleeding Rate* (bleeding episodes per year per subject)</b>	8.0 (12.2, 15.4)	0.0 (0.6, 1.4)
<b>Annualized FVIII Use Rate* (infusions per year per subject)</b>	155.5 (146.5, 41.6)	0.0 (2.0, 4.8)

\*Post-infusion data were based on data after Week 4.

#### Efficacy Data on 6e13 vg/kg Dose as Presented at ASH

As of the Nov. 16, 2017 data cutoff, all seven patients at the 6e13 vg/kg dose had been followed for at least 78 weeks post infusion. Median and mean Factor VIII levels from week 20 through 78 for the 6e13 vg/kg dose cohort have been consistently within the normal range, expressed as a percentage of normal factor activity in blood. At 78 weeks post infusion, the median and mean Factor VIII levels of the 6e13 vg/kg cohort are 90 and 89% respectively. Median annualized bleed and factor VIII use rates for the 6e13 vg/kg were zero after Week 4. After 52 weeks of follow-up, the phase 1/2 study protocol specified that planned patient visits were reduced in frequency from once every one to two weeks to once every three months. Consequently, as of May 31, 2017 when all patients in the 6e13 vg/kg dose had reached 52 weeks of follow up, all patients in the 6e13 vg/kg dose converted to a quarterly follow-up visit schedule.

#### Factor VIII Levels (%) of 6e13 vg/kg Dose Patients\* by Visit (N=7) at Nov. 16, 2017 data cut

Week**	<b>20</b>	<b>24</b>	<b>28</b>	<b>32</b>	<b>36</b>	<b>40</b>	<b>44</b>	<b>48</b>	<b>52</b>	<b>65</b>	<b>78</b>
6e13 vg/kg Dose											
N***	7	7	7	6	7	7	7	7	7	7	7
Median Factor VIII Level**** (%)	<b>97</b>	<b>101</b>	<b>122</b>	<b>99</b>	<b>99</b>	<b>111</b>	<b>105</b>	<b>105</b>	<b>89</b>	<b>98</b>	<b>90</b>
Mean Factor VIII Level**** (%)	<b>118</b>	<b>129</b>	<b>123</b>	<b>122</b>	<b>116</b>	<b>124</b>	<b>122</b>	<b>106</b>	<b>104</b>	<b>93</b>	<b>89</b>
Range (low, high)	(12, 254)	(12, 227)	(15, 257)	(26, 316)	(31, 273)	(17, 264)	(20,242)	(23,195)	(20, 218)	(16,145)	(11,179)

\*All patients had severe hemophilia A at baseline, defined as less than or equal to 1% of Factor VIII activity levels, expressed as a percentage of normal factor activity in blood.

\*\*Weeks were windowed by +/- 2 weeks and after 52 weeks, measurements were taken every 3 months

\*\*\* For week 32, one patient did not have a Factor VIII activity level available.

\*\*\*\*Bolded numbers are in the normal range of Factor VIII as defined by the World Federation of Hemophilia, <http://www.wfh.org/en/page.aspx?pid=643> (link current as of Dec. 6, 2017). Factor VIII levels are determined by one-stage assay.

**Valoctocogene Roxaparvovec Reduces Bleeds and Factor VIII Use: Summary of Annualized Bleeding Rate (ABR) and FVIII Infusions of 6e13 vg/kg Dose Patients Previously on Prophylaxis (N=6)\* at Nov. 16, 2017 data cut**

	Before valoctocogene roxaparvovec Infusion***	After valoctocogene roxaparvovec Infusion****
	Median (mean, SD)	Median (mean, SD)
<b>Annualized Bleeding** Rate(bleeding episodes per year per subject)</b>	16.5 (16.3, 15.7)	0.0 (0.5, 1.2)
<b>Annualized FVIII Infusions** (infusions per year per subject)</b>	138.5 (136.7, 22.4)	0.0 (6.1, 14.9)

\*A 7<sup>th</sup> patient received Factor VIII on demand and was not included in analysis.

\*\*Post infusion data were based on data after Week 4

\*\*\*Obtained from medical records.

\*\*\*\*5 of 6 patients had 0 bleeds requiring Factor VIII infusions and 0 Factor VIII infusions after Week 4.

**Quality of Life (QoL)**

Patients who received the 6e13 vg/kg dose demonstrated improved total scores when assessed with the Haemo-QoL-A questionnaire, a validated health-related quality of life (hrQoL) measurement tool for patients with hemophilia, as early as 16 weeks, with maintenance of hrQoL scores above the minimal clinically important difference (MCID) range (i.e., total score increase of 5.2 to 7.9, based on prior studies) through 78 weeks after receiving a single dose of valoctocogene roxaparvovec. By week 16, patients achieved a clinically meaningful improvement from baseline, with a mean hrQoL score increase of 13.4 and a standard deviation (SD) of 11.2. At week 78, the mean hrQoL score increase was 16.6 with an SD of 11.9. The improvements above the MCID range of the Haemo-QoL-A total scores were supported by improvements achieved across all six domains tested, i.e. Consequences of Bleeding, Physical Functioning, Role Functioning, Emotional Impact, Treatment Concern, and Worry.

**Change from Baseline in Total Health-Related Quality of Life (hrQoL) Score of 6e13 vg/kg Dose Cohort at Nov. 16, 2017 data cut**

		6E13 vg/kg Dose Cohort (N=7)	
		Total hrQoL Score	Change from Baseline
<b>Baseline</b>	Mean (SD)	71.9 (16.6)	(na)
	Median	76.2	(na)
<b>Week 16</b>	Mean (SD)	85.3 (13.0)	13.4 (11.2)
	Median	84.7	6.0
<b>Week 28</b>	Mean (SD)	84.8 (12.5)	12.9 (13.7)
	Median	87.5	8.0
<b>Week 52</b>	Mean (SD)	81.6 (15.1)	9.6 (12.7)
	Median	86.7	7.0
<b>Week 78 (n=5)</b>	Mean (SD)	80.6 (14.4)	16.6 (11.9)
	Median	87.6	13.7

SD = standard deviation; na = not applicable.

**New England Journal of Medicine Publishes 1 Year Data on 6e13 vg/kg Dose Data**

The company also announced that the *New England Journal of Medicine* (NEJM) published an independent peer-reviewed article on the ongoing Phase 1/2 study to evaluate safety and efficacy of investigational gene therapy, valoctocogene roxaparvovec, at the 6e13 dose in men with severe hemophilia A at 52 weeks.

The NEJM article, "AAV Gene Transfer in Patients with Severe Hemophilia A," concluded that valoctocogene roxaparvovec is associated with the "sustained normalization" of Factor VIII activity over a period of one year in six of seven study participants who received the 6e13 vg/kg dose with stabilization of hemostasis and a "profound" reduction in Factor VIII use in all seven participants. The article also concluded that safety findings were limited to elevations in liver function tests and notes the relatively small sample size. For additional safety data, see *Safety* section in press release.

## **Valoctocogene Roxaparvovec Safety**

Overall, valoctocogene roxaparvovec has been well-tolerated by patients across all doses, including the two patients who received the lowest doses of  $6 \times 10^{12}$  and  $2 \times 10^{13}$  vg/kg, respectively. No patients developed inhibitors to Factor VIII, and no patients withdrew from the study. The most common adverse events (AEs) across all dose cohorts were alanine aminotransferase (ALT) elevation (11 patients, 73%); arthralgia (9 patients, 60%); aspartate aminotransferase elevation (8 patients, 53%); headache (7 patients, 47%); back pain, fatigue and upper respiratory tract infection (5 patients, 33%). Two patients reported serious adverse events (SAEs) during the study. One patient was hospitalized for observation after developing Grade 2 pyrexia with myalgia and headache within 24 hours of receiving valoctocogene roxaparvovec. The event resolved within 48 hours following treatment with paracetamol, an over-the-counter treatment for pain and fever. The event was assessed as related to valoctocogene roxaparvovec. The other SAE was assessed as not related to valoctocogene roxaparvovec, attributed to a planned knee surgery to treat hemophilic arthropathy, and Grade 1 in severity. No complications were reported.

## **Upcoming GENER8 Studies**

The global Phase 3 program includes two studies with valoctocogene roxaparvovec, one with the  $6 \times 10^{13}$  vg/kg dose (GENER8-1) and one with the  $4 \times 10^{13}$  vg/kg dose (GENER8-2). Both Phase 3 GENER8 studies will be open-label single-arm studies to evaluate the efficacy and safety of valoctocogene roxaparvovec. GENER8-1 will enroll its first patient this month, and GENER8-2 will enroll the first patient at the start of 2018. The primary endpoint will be a change from baseline FVIII activity level, and the secondary endpoints will measure annualized FVIII replacement therapy use rate and annualized bleed rate.

BioMarin will also begin a Phase 1/2 Study with the  $6 \times 10^{13}$  vg/kg dose and with approximately 10 patients who are AAV5 positive. The first patient is expected to enroll in the first half of 2018.

## **Regulatory Status**

The U.S. Food and Drug Administration (FDA) granted valoctocogene roxaparvovec Breakthrough Therapy Designation. The FDA's Breakthrough Therapy Designation program is intended to facilitate and expedite development and review of new drugs to address unmet medical need in the treatment of a serious condition. To qualify for Breakthrough Therapy Designation, preliminary clinical evidence must show that the drug may demonstrate substantial improvement over existing therapies.

The European Medicines Agency (EMA) has granted access to its Priority Medicines (PRIME) regulatory initiative for valoctocogene roxaparvovec. To be accepted for PRIME, an investigational therapy has to show its potential to benefit patients with unmet medical needs based on early clinical data. PRIME focuses on medicines that may offer a major therapeutic advantage over existing treatments, or benefit patients with no treatment options. These medicines are considered priority medicines within the European Union (EU).

BioMarin's valoctocogene roxaparvovec has also received orphan drug designation from the FDA and EMA for the treatment of severe hemophilia A. The Orphan Drug Designation program is intended to advance the evaluation and development of products that demonstrate promise for the diagnosis and/or treatment of rare diseases or conditions.

## **Gene Therapy Manufacturing**

BioMarin has constructed one of the largest gene therapy manufacturing facilities in the world, which is located in Novato, California. Good Manufacturing Practices (GMP) production of valoctocogene roxaparvovec has commenced and will support clinical development activities and anticipated commercial demand. This facility is capable of supporting approximately 2,000 patients per year, and the production process was developed in accordance with International Conference on Harmonisation guidance for Pharmaceuticals for Human Use facilitating worldwide registration with health authorities.

## **About Hemophilia A**

Hemophilia A, also called Factor VIII (FVIII) deficiency or classic hemophilia, is a genetic disorder caused by missing or defective Factor VIII, a clotting protein. Although it is passed down from parents to children, about 1/3 of cases are caused by a spontaneous mutation, a new mutation that was not inherited. As an X-linked disorder, hemophilia A mostly affects males, occurring in approximately 1 in 5,000 male births. People living with the disease are not able to form blood clots efficiently and are at risk for excessive bleeding from modest injuries, potentially endangering their life. People with severe hemophilia often bleed spontaneously into their muscles or joints. The standard of care for the 43% of hemophilia A patients who are severely affected, is a prophylactic regimen of Factor VIII infusions three times per week. Even with prophylactic regimens, many patients still experience microbleeds and spontaneous bleeding events that result in progressive joint damage.

## About BioMarin

BioMarin is a global biotechnology company that develops and commercializes innovative therapies for patients with serious and life-threatening rare and ultra-rare genetic diseases. The company's portfolio consists of six commercialized products and multiple clinical and pre-clinical product candidates. For additional information, please visit [www.biomarin.com](http://www.biomarin.com). Information on BioMarin's website is not incorporated by reference into this press release.

## Forward Looking Statement

This press release contains forward-looking statements about the business prospects of BioMarin Pharmaceutical Inc., including without limitation, statements about the development of BioMarin's valoctocogene roxaparvovec program generally, the impact of valoctocogene roxaparvovec gene therapy for treating patients with severe hemophilia A, the potential for valoctocogene roxaparvovec to bring Factor VIII levels to normal and to reduce or eliminate bleeds, the planned Phase 3 studies, the planned Phase 1/2 study, or other possible future clinical studies of valoctocogene roxaparvovec. These forward-looking statements are predictions and involve risks and uncertainties such that actual results may differ materially from these statements. These risks and uncertainties include, among others: results and timing of current and planned preclinical studies and clinical trials of valoctocogene roxaparvovec, including final analysis of the above interim data; any potential adverse events observed in the continuing monitoring of the patients in the Phase 1/2 trial; the content and timing of decisions by the U.S. Food and Drug Administration, the European Commission and other regulatory authorities; the content and timing of decisions by local and central ethics committees regarding the clinical trials; our ability to successfully manufacture the product candidate for the preclinical and clinical trials; and those other risks detailed from time to time under the caption "Risk Factors" and elsewhere in BioMarin's Securities and Exchange Commission (SEC) filings, including BioMarin's Quarterly Report on Form 10-Q for the quarter ended September 30, 2017, and future filings and reports by BioMarin. BioMarin undertakes no duty or obligation to update any forward-looking statements contained in this press release as a result of new information, future events or changes in its expectations.

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